*The synergistic effect of anticholinergic burden and depression on fall risk in older persons.*

Running title: *ACB, depression and fall risk.*

**Authors:**

**Raymond Salet1, Nathalie van der Velde2, 4, Didi Rhebergen3, 4, 5, Bob van de Loo2, 4, 7, Lotta Seppala2, Natasja M. van Schoor4, 7, Bruno Stricker6, Marieke Henstra2**

Corresponding author: Raymond Salet, r.w.j.salet@umcutrecht.nl

Affiliations:

1: University Medical Centre Utrecht, Department of Psychiatry, Utrecht, The Netherlands

2: Amsterdam UMC location University of Amsterdam, Internal Medicine, Section of Geriatric Medicine, Amsterdam, The Netherlands.

3: Mental Health Care Institute GGZ Centraal, Amersfoort, The Netherlands.

4: Amsterdam Public Health Research Institute, Aging and Later Life, Amsterdam, The Netherlands.

5. Amsterdam UMC location VUmc, Section of Psychiatry, Amsterdam, The Netherlands.

6: Erasmus University Medical Centre, Department of Epidemiology and Biostatistics, Rotterdam, The Netherlands

7: Amsterdam UMC location VUmc, Department of Epidemiology and Data Science, Amsterdam, The Netherlands

**Key words:**

Anticholinergic burden, depression, fall risk, older persons

Word count: 3987 words

Table count: 4

Figure count: 1

**Author contribution statement**

Raymond Salet, Nathalie van der Velde and Marieke Henstra contributed to the study conception and design. Data was collected and prepared by Bob van de Loo. Raymond Salet analyzed the data in close collaboration with Marieke Henstra. Raymond Salet wrote the first draft of the manuscript and all authors commented on previous versions of the manuscript. All authors read and approved the final manuscript. All authors Agreed to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

***What is already known about this subject:***

* Both anticholinergic burden and depression increase fall risk in older persons.
* However, the effect of depression on fall risk associated with ACB is unclear.
* This is relevant because many psychotropics have anticholinergic properties.

***What this study adds:***

* There is a positive interaction between depression and anticholinergic burden on fall risk in older persons, meaning fall risk is higher when both risk factors are present than expected from the combination of those risk factors.
* This stresses the importance of considering anticholinergic burden when choosing pharmacological treatment for depression.

**Abstract:**

**Aim**:

Both anticholinergic burden (ACB) and depression are known to increase fall risk in older persons, next to increasing morbidity and mortality. However, the effect of depression on fall risk associated with ACB is unclear. This is relevant because most antidepressants have anticholinergic effects. The aim of this study was to assess the relationship between ACB and falls, and the impact of depression on this relationship.

**Methods:**

We cross-sectionally examined the relationship between both ACB and clinical depression and falls in the past 12 months, in a harmonized cohort of Dutch community dwelling persons (n=7884). For all analyses, we calculated adjusted odds ratios (ORs) and their 95% confidence intervals. We also investigated the impact of depression on the relationship between ACB and falls, by calculating interaction on both an additive and multiplicative scale.

**Results:**

Both a high ACB score (≥3) and clinical depression were independently significantly associated with falls in the past 12 months. Additionally, there was a statistically significant interaction (p=0.038) between ACB and clinical depression on fall risk, both on an additive and multiplicative scale (1.13 and 1.44 respectively).

**Conclusion:**

In older persons, the presence of clinical depression strengthened the association between ACB and falls. We dissuade bluntly withholding pharmacological treatment to avoid falls, despite the ACB of antidepressants. In case of depression, we recommend considering non-pharmacological alternatives; choose pharmacological interventions with the lowest risk of adverse events; assess and treat other fall risk-factors; and perform multidisciplinary a medication review to minimize (accumulation of) ACB.

1. **Introduction**

In older persons, both depression and the use of medications with anticholinergic properties are important risk factors for fall incidents, a major health concern in the aging population. The underlying mechanisms of increased fall risk caused by depressive symptoms are multifactorial, and among others mediated through deconditioning, apathy, psychomotor retardation, impaired attention, insufficient sleep and muscle weakness [1-3]. Next, older persons with depression often suffer from multiple chronic conditions, for example pain and cardiovascular diseases [4]. Medications for these and multiple other common conditions often have anticholinergic properties [5]. As a result, there is a risk of anticholinergic burden (ACB) accumulation in this population particularly due to clinicians' lack of awareness. Medications with anticholinergic properties are also known to increase fall risk and even risk of hospitalization [6], especially in vulnerable older populations [5]. The increased fall risk due to anticholinergic medication is probably mediated through impaired coordination, gait, sedation, balance, confusion, and blurred vision [7].

Virtually all drugs used to treat depression have anticholinergic properties, however, they vary between subclasses. For example, tricyclic antidepressants (TCAs), the preferred medications for the treatment of severe major depressive disorder (MDD), have stronger anticholinergic adverse effects than selective serotonin reuptake inhibitors (SSRIs) and serotonin norepinephrine reuptake inhibitors (SNRIs). Furthermore, also antipsychotic medications with anticholinergic properties, e.g. second generation antipsychotics such as olanzapine, can be prescribed during the treatment of depression. For example, to treat comorbid psychotic symptoms, or as adjuvants if treatment response to antidepressants is insufficient. So, it is clear that pharmacological treatment of depression may increase fall risk [2] but it is unclear whether there is a synergistic negative effect of drug-disease interaction on fall risk (e.g. usage of anticholinergic medications and depressive symptoms combined).

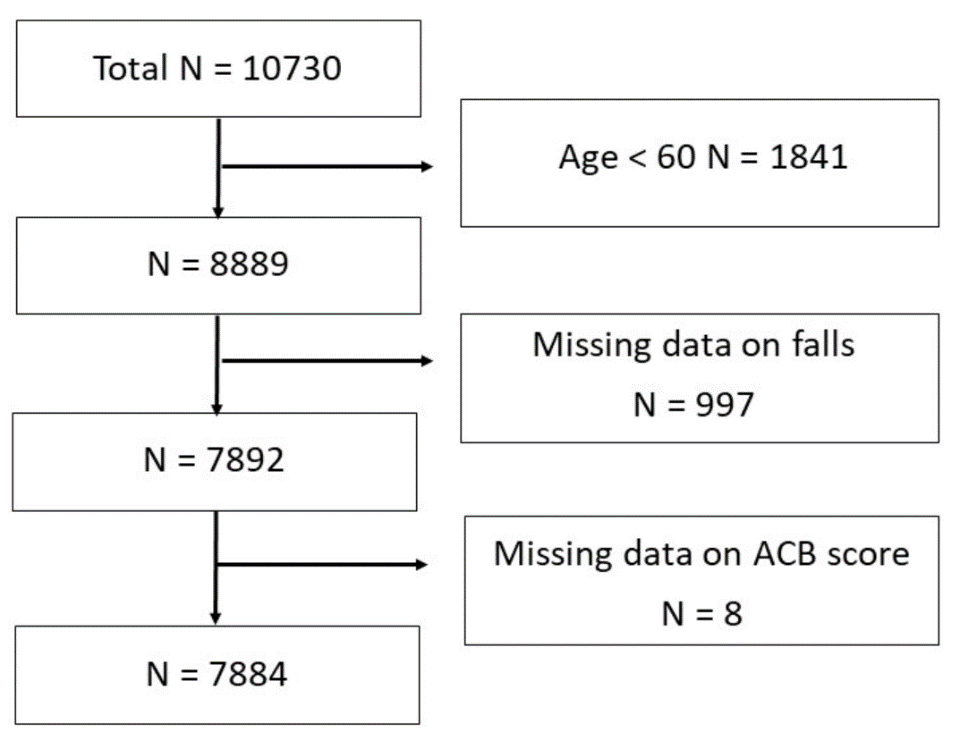
Therefore, our study intends to increase the knowledge on the relationship between anticholinergic burden, depressive symptoms and fall risk. The main aim of our study is to investigate the impact of depression on the association between anticholinergic burden and fall incidents in a retrospective cross-sectional study using the data of three cohorts of the AD*F*ICE\_IT harmonized dataset [8]. We hypothesize that the anticholinergic burden is associated with fall incidents and that this association is stronger in co-occurrence of depression. Furthermore, we will also assess the association between depression and falls. Better understanding of how depression affects ACB-related fall risk will help clinicians to weigh the benefits and harms of pharmacological treatment of depression in older persons with regard to fall risk.

1. **Methods**

Study population

For this study data was used from three cohorts of the AD*F*ICE\_IT harmonized cohort data set [8]. The total data set includes 6 cohort studies, of which one has two separate waves, which all gathered retrospective data on both fall incidents and depressive symptoms. Three of the included cohorts comprised data on both the Center for Epidemiological Studies Depression scale (CES-D) score and anticholinergic burden [8] and were therefore suitable for our study. These were part of the Longitudinal Aging Study Amsterdam (LASA) and the Rotterdam Study, which both include older persons, either community dwelling or receiving institutionalized care. The LASA data was collected in two separate cohorts in 1995-1996 and 2012-2013 (waves C and 3B respectively), and from the Rotterdam study the ERGO-5 cycle was used, the data being collected between 2009 and 2013. Participants from all cohorts provided informed consent, and all cohort studies were approved by their institutional ethics committees. Detailed information on the cohorts has been published elsewhere [9, 10].

For the present study, individuals aged ≥ 60 with complete data on both anticholinergic burden and fall incidents were included (n=7884). Details on the inclusion process are depicted in Figure 1.



**Figure 1** Inclusion process of the study sample

Measurements

Anticholinergic burden (ACB)

For the assessment of the anticholinergic burden, the ACB-scale [11] was used. This scale scores each medication with a range of 0-3 depending on its anticholinergic properties. The ACB score is validated and considered being the highest quality anticholinergic burden scale [12]. It is the most commonly used tool for scoring anticholinergic burden [13]. For each used substance the ACB score was determined. Next, the total ACB score was calculated for each person. The process of collecting the medication data is described in covariates.

In previous studies, the ACB score is commonly expressed as a categorical variable. However, there is inconsistency in the existing literature on how to categorize ACB scores [6, 7, 14-17]. In our study, only 235 (3.0%) of the participants had a score of four or higher. We therefore created five categories for the assessment of the association between ACB and falls: ACB = 0, ACB = 1, ACB = 2, ACB = 3 or ACB ≥ 4.

Next, to calculate the degree of interaction we dichotomized the ACB (0-1 and ≥2). Literature is inconclusive on what level of ACB increases fall risk [7, 16-19]. The ACB score of 1 is defined as having only an in vitro effect, so medication with this score should not have a relevant clinical effect[11]. Furthermore, a review by Stewart et al. concluded that the relationship between lower levels of ACB and falls was inconclusive, but an ACB of 2 (moderate) or higher poses a higher fall risk among older people [18].

Falls in the past 12 months

We assessed falls in the past 12 months as a dichotomous variable. This data was collected at baseline by asking the participant whether and if yes, how often they had fallen in the last 12 months. Both the Rotterdam Study and LASA collected this data in an interview.

Depression

For depressive symptoms the twenty-item Center for Epidemiologic Studies Depression scale (CES-D) was used, measuring core symptoms of depression in the past week. Responses were rated on a 4-item scale, ranging from 0 to 3. The scale ranges from 0-60 with a score over 16 indicating clinically relevant depressive symptoms, henceforth called ‘clinical depression’. The CES-D has good reliability and validity for screening depressive symptoms across age [20].

Covariates

Sex, age, education, cognitive functioning, Body Mass Index (BMI), blood pressure, alcohol use, smoking, number of medications, medications with sedative properties (opioids, benzodiazepines, antidepressants and antipsychotics) were included as covariates. These covariates were selected because literature shows they increase fall risk [21]. Education was measured as highest level of education completed. In case of uncertainty, an equivalent was determined by the number of years attained. Cognitive functioning was assessed with the Mini Mental State Examination (MMSE) [22]. BMI was based on measured weight in kilograms divided by height in meters squared. Blood pressure was measured in mmHg in duplicate at the upper arm in sitting position, after which the mean was calculated. Alcohol use was quantified using both the self-reported frequency of consumption of alcoholic beverages per day, week or month, and the number of consumptions per day drinks taken. The frequency and amount per time were combined in a standardized severity score, this is described in detail in Supplementary File 1. Smoking was measured as either never, former or current smoker, also by self-report. Medication use was registered by all cohorts by asking participants to show the medications they used on the day of the home interview [9, 10]. Medications were registered using ATC codes [23]. Supplementary file 2 contains a list of all ATC codes of medications with anticholinergic properties.

Medications with sedative properties were grouped into opioids (ATC codes N02A, N02BA51, N02BE51 and M01AE51), benzodiazepines (ATC codes N05BA, N05CD and N05CF), antidepressants (ATC codes N06AA, N06AB, N06AF, N06AG, N06AX N06CA01, N06CA02 and N06CA03) and antipsychotics (ATC codes N05A). The variables education level, smoking status and alcohol intake were harmonized due to different assessments per cohort.

Statistical analysis

All statistical analyses were performed using IBM SPSS Statistics version 29.0.1. The distribution of baseline characteristics was examined across persons with or without falls in the last 12 months (y/n). All continuous variables were non-normally distributed and therefore examined through the non-parametric Mann-Whitney U test. The 2 test was used for categorical variables. A confidence interval of 95% was computed and p-values < .05 were considered statistically significant.

We performed multiple imputation because three values had over 1% missing data: CES-D (5.4%), BMI (10.4%) and mean systolic blood pressure (12.0%). For imputation, we used eleven baseline variables (age, sex, ACB score, education level, alcohol intake, smoking status, number of medications, opioid use, benzodiazepine use, SSRI use and TCA use). Because the largest percentage of missing data was 12%, ten data sets were used [24].

Next, we examined the association between ACB and falls in the past 12 months (y/n), using binary logistic regression analysis. The ACB score of 0 was used as reference. We calculated odds ratios (ORs) and their 95% confidential intervals (95% CI). To assess putative confounding, we firstly created a basic model containing age and sex (Model 1). Next, potential confounders were added to Model 1 separately. If there was a change of ≥10% in the regression coefficient, the confounder was incorporated in the adjusted model (Model 2). For the association between clinical depression and falls in the past 12 months we followed a similar procedure except that we also investigated ACB as a possible confounder. To avoid multicollinearity, the variation inflation factor (VIF) was calculated for all variables. A VIF higher than 5 was considered to indicate considerable collinearity. All VIF values were below 5 (range 1.02 to 2.44).

We examined the interaction between ACB and clinical depression by adding the product-term of the dichotomous variables ((ACB ≥ 2)\*clinical depression) to the basic model along with ACB ≥ 2 and clinical depression as independent variables. Interaction was considered present if the product-term had a p-value < 0.10 [25]. Because in our study interaction was present, both additive and multiplicative interaction were then calculated, in order to examine the direction (positive or negative) and magnitude of the interaction [26-28]. To do this, firstly separate OR’s were calculated for the subgroups of patients 1) with clinical depression but without ACB ≥ 2 (OR10), 2) without clinical depression but with ACB ≥ 2 (OR01) and 3) with both clinical depression and ACB ≥ 2 (OR11). All OR’s were calculated using the subgroup with neither clinical depression nor ACB ≥ 2 (OR00) as reference (table 4). For the assessment of additive interaction (also referred to as “relative excess risk due to interaction” or RERI) we used the following formula: *RERI = OR11 - OR10 - OR01  + 1.* A RERI of > 0 is indicative for a positive interaction, a RERI of < 0 indicates negative interaction. In order to calculate multiplicative interaction, we used the formula *OR11/(OR10\*OR01).* A result of < 1 indicates a negative interaction (or weakening effect), if > 1 the interaction is considered to be positive (a strengthening effect).

Finally, unfortunately 5.530 (70%) of the MMSE scores were missing (distribution of missings: Rotterdam 93.6%, LASA 0.2%). We therefore were unable to impute this variable. To investigate potential selection bias, we investigated MMSE as a confounder in the LASA cohort and performed our analyses stratified for the two subsamples in a sensitivity analysis (Supplementary File 1).

1. **Results**

Baseline characteristics, presented across presence of falls in the past 12 months (y/n), are described in table 1. Of the total sample, median age was 72 years (IQR 66-79) and 4470 (56.7%) were women. The median ACB score was 0 (IQR 0-1), the median CES-D score was 4 (IQR 1-9) and 820 (11%) had a CES-D score above the cut off for clinical depression. 2081 participants (26.4% of the study sample) experienced a fall in the past 12 months. Participants in this group were significantly more often female, older, had a higher ACB score, a higher CES-D score, higher education level, drank less alcohol, used more medications, opioids, benzodiazepines, antidepressants and antipsychotics compared with non-fallers.

*The association between ACB and falls in the past 12 months (y/n)*

An ACB score of 1 was not associated with falls in the past 12 months in either model (table 2). An ACB score of 2 was associated with falls in model 2, but not statistically significantly (OR 1.16; 95% CI 0.94 – 1.43). ACB scores of 3 and above had a statistically significant positive association with an increased fall risk in model 2 (table 2). Furthermore, there is an incremental increase in the strength of the association, with higher ACB scores being significantly, and stronger associated with fall risk as compared to lower ACB-scores.

*The association between clinical depression and falls in the past 12 months (y/n)*

Clinical depression was associated with falls in the past 12 months in both models

(model 1 OR 1.55; 95% CI 1.34-1.79, model 2 OR 1.44; 95% CI 1.24 – 1.68, table 3).

*The interaction between ACB and clinical depression on falls in the past 12 months (y/n)*

There was a significant interaction between clinical depression and ACB in the basic regression model (p = 0.038). The interaction on additive scale (RERI) was 1.13, meaning the OR for the combination of both risk factors is 1.13 points higher than expected when adding the individual OR’s. When calculating interaction on a multiplicative scale, the OR for the combination of clinical depression and ACB was found to be 1.44 times higher than expected when multiplying the individual OR’s (table 4, 2.10 vs 3.03).

*Sensitivity analyses*

In the LASA cohorts, MMSE was not a confounder in the association between ACB nor clinical depression and falls in the past 12 months; changes of regression coefficient were 4% and 1% respectively (table 1 and 3 Supplementary File 1). In the LASA cohort, the OR of the association between ACB and falls in the past 12 months using model 2 was 1.01 (95% CI 0.89 - 1.14, table 2 Supplementary File 1), when MMSE was added to the model the OR was practically unchanged: 1.01 (95% CI 0.89 - 1.15, table 2 Supplementary File 1). For clinical depression, the OR in model 2 was 1.14 (95% CI 0.86 - 1.51, table 4 Supplementary File 1), and after adding the MMSE score to the model, the OR was unchanged 1.14 (95% CI 0.86 - 1.51, table 4 Supplementary File 1). Because of this minimal change, we assume that in case of sufficient data on the MMSE of the Rotterdam cohort, its’ impact on our results would be negligible. **Table 1: Baseline characteristics (non-imputed dataset)**

|  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- |
| Characteristic | % Missing | Total (n= 7884) | Fall No (n= 5801) | | Fall yes (n=2083) | | P value |
| Sexa (% men) | 0 | 3411 (43.3) | | 2608 (45.0) | | 803 (38.6) | <0.001 |
| Age (years) | 0 | 72 (66-79) | | 71 (66-78) | | 73 (67-80) | <0.001 |
| ACB Score (points, continuous) | 0 | 0 (0-1) | | 0 (0-1) | | 0 (0-1) | <0.001 |
| ACB (points, categorized) |  |  | |  | |  | <0.001 |
| ACB 0 (%) | 0 | 5129 (65.1) | | 3876 (66.8) | | 1253 (60.2) |  |
| ACB 1 (%) | 0 | 1635 (20.7) | | 1199 (20.7) | | 436 (20.9) |  |
| ACB 2 (%) | 0 | 542 (6.9) | | 365 (6.3) | | 177 (8.5) |  |
| ACB 3 (%) | 0 | 343 (4.4) | | 227 (3.9) | | 116 (5.6) |  |
| ACB ≥4 (%) | 0 | 235 (3.0) | | 134 (2.3) | | 101 (4.8) |  |
| CES-D Score (points) | 5.4 | 4 (1-9) | | 3 (1-8) | | 5 (2-12) | <0.001 |
| Clinical depressiona (CES-D > 16, %) | 5.4 | 823 (11.0) | | 522 (9.4) | | 301 (15.6) | <0.001 |
| MMSE | 70.3 | 27 (25-29) | | 28 (25-29) | | 27 (25-29) | 0.041 |
| BMI (kg/m2) | 10.4 | 27.0 (24.5-29.7) | | 26.9 (24.5-29.6) | | 27.0 (24.4-30.1) | 0.434 |
| Systolic blood pressure (mmHg) | 12.0 | 146 (132-162) | | 146 (132-162) | | 146 (132-162) | 0.667 |
| Education levela | 0.9 |  | |  | |  | 0.010 |
| High (%) |  | 1381 (17.7) | | 3184 (55.4) | | 1224 (58.8) |  |
| Average (%) |  | 2025 (25.9) | | 1526 (26.5) | | 499 (24.0) |  |
| Low (%) |  | 4408 (56.4) | | 1038 (18.1) | | 343 (16.5) |  |
| Alcohol intakea | 0.2 |  | |  | |  | 0.044 |
| Non (%) |  | 1411 (17.9) | | 998 (17.2) | | 413 (19.9) |  |
| Rarely (%) |  | 1136 (14.4) | | 823 (14.2) | | 313 (15.1) |  |
| Low risk (%) |  | 4090 (52.0) | | 3047 (52.6) | | 1043 (50.2) |  |
| Medium risk (%) |  | 953 (12.1) | | 717 (12.4) | | 236 (11.4) |  |
| High risk (%) |  | 275 (3.5) | | 204 (3.5) | | 71 (3.4) |  |
| Smoking statusa | 0.2 |  | |  | |  | 0.430 |
| Never (%) |  | 2683 (34.0) | | 1930 (33.3) | | 753 (36.2) |  |
| Former (%) |  | 4153 (52.7) | | 3081 (53.2) | | 1072 (51.6) |  |
| Current (%) |  | 1033 (13.1) | | 779 (13.5) | | 254 (12.2) |  |
| Number of medications | 0 | 3 (1-5) | | 2 (1-5) | | 3 (1-5) | <0.001 |
| Opioidsa (% yes) | 0 | 325 (4.1) | | 211 (3.6) | | 114 (5.5) | <0.001 |
| Benzodiazepinesa (% yes) | 0 | 745 (9.4) | | 497 (8.6) | | 248 (11.9) | <0.001 |
| Antidepressantsa (% yes) | 0 | 470 (6.0) | | 296 (5.1) | | 174 (8.4) | <0.001 |
| SSRIa (% yes) | 0 | 242 (3.1) | | 153 (2.6) | | 89 (4.1) | <0.001 |
| TCA (% yes) | 0 | 149 (1.9) | | 92 (1.6) | | 57 (2.7) | 0.001 |
| Antipsychoticsa (% yes) | 0 | 66 (0.8) | | 40 (0.7) | | 26 (1.2) | 0.016 |

Values presented are median (interquartile range, IQR) for continuous data and number (%) for categorical data.

*ACB* Anticholinergic Cognitive Burden *CES-D* Center for Epidemiologic Studies Depression Scale *BMI* Body Mass Index *MMSE* Mini Mental State Examination *SSRI* Selective Serotonin Reuptake Inhibitor *TCA* Tricyclic Antidepressant

a: Presented as percentages, differences tested using Chi-square test

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| **Table 2: Association between ACB score and falls in the past 12 months** | | | | | | |
|
|  | **Model 1 (crude)** | | | **Model 2 (adjusted)** | | |
|  | OR | 95% CI | p-value | OR | 95% CI | p-value |
| ACB 0 | Reference | | | Reference | | |
| ACB 1 | 1.04 | 0.92 – 1.19 | 0.514 | 0.96 | 0.83 – 1.10 | 0.765 |
| ACB 2 | 1.34 | 1.10 – 1.63 | 0.152 | 1.16 | 0.94 – 1.43 | 0.061 |
| ACB 3 | 1.47 | 1.17-1.86 | 0.001 | 1.27 | 1.00 – 1.63 | 0.054 |
| ACB ≥ 4 | 2.18 | 1.67 – 2.85 | <0.001 | 1.79 | 1.34 – 2.40 | <0.001 |
|  | | | | | | |

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| **Table 3: Association between clinical depression and falls in the past 12 months** | | | | | | |
|
|  | **Model 1 (crude)** | | | **Model 2 (adjusted)** | | |
|  | OR | 95% CI | p-value | OR | 95% CI | p-value |
| Clinical depression | 1.62 | 1.38 – 1.90 | <0.001 | 1.51 | 1.29 – 1.77 | <0.001 |
|  | | | | | | |

|  |  |  |
| --- | --- | --- |
| Table 4: Odds ratios of falls in the past 12 months, with 95% confidence intervals, used for calculating interaction | | |
|  | **ACB < 2** | **ACB ≥ 2** |
| No clinical depression | Reference (OR00) | 1.37; 95% CI 1.36 - 1.40 (OR01) |
| Clinical Depression | 1.53; 95% CI 1.51 - 1.55 (OR10) | 3.03; 95% CI 3.02 - 3.08 (OR11) |

1. **Discussion**

In this cross-sectional study using harmonized data of two large community-based cohorts on older persons, we found that usage of anticholinergic medications and clinical depression were associated with falls in the past 12 months. Furthermore, the association between ACB and fall risk was stronger for higher ACB scores, and absent for the ACB score of one and two. Besides this, there was a positive interaction between ACB ≥ 2 and clinical depression on both additive and multiplicative scale, meaning the risk of falls in older persons with both ACB and clinical depression was higher than expected from the combination of those individual risk factors.

Our finding that clinically relevant depressive symptoms and ACB score interact positively on falls in the past 12 months, has not been reported previously to our knowledge. We reason this may be explained by the fact that depressive symptoms such as apathy, inactivity and muscle weakness, may potentiate the impact of anticholinergic burden. This may cause a negative synergistic effect further increasing the risk of falls. This means patients with depression who are prescribed medications with anticholinergic properties, such as most psychotropics [11], have an even higher fall risk than previously thought.

The association between a higher anticholinergic burden and increased fall risk has been clearly established in previous studies [29]. However, because of the heterogeneity of different anticholinergic scoring systems, study designs, and study populations it is a difficult to quantify the fall risk associated with the ACB score [29], which makes it difficult to compare our findings to previous studies. Taking this into account, our results are nevertheless roughly comparable with previous studies [18], although we did not find an independent statistically significant effect of an ACB of 2 on fall risk. Next, our finding that clinically relevant depressive symptoms are associated with an increased fall risk is also in line with previous studies [14, 21]. Meta-analysis showed a 37% increased risk related to depression [21].

An interesting question is how to optimally target both risk factors. As mentioned, depression in older persons causes a high burden of disease and has been previously been associated with morbidity and mortality. Prompt detection and treatment of depression in older persons is advisable. In case of severe depression, treatment with medication with anticholinergic load is generally needed. If so, a personalized consideration is necessary for each individual [3]. Namely, effectiveness should be the first consideration when choosing an antidepressant [3], however antidepressants from the same subclass may be equally effective whilst differing strongly in their anticholinergic properties [30]. Besides the anticholinergic adverse effects, all other adverse effects should be considered in clinical decision making [3]. Also, clinicians need to be aware of the use of both other fall risk inducing drugs (FRIDs) as well as the risk of accumulation of ACB. Older persons with depression often suffer from multiple other chronic conditions and therefore may use other medications with anticholinergic properties besides the psychotropic medications.

Besides pharmacological treatment of the depression, we recommend clinicians to explore non-pharmacological interventions. Namely, non-pharmacological interventions, such as psychotherapeutic treatments like cognitive behavioral therapy, have been shown to be effective in older persons [31, 32], with results comparable to those observed in middle-aged adults [31]. Physical exercise has the advantage to both decrease fall risk [21] and reduce depressive symptoms [33]. Next, cognitive behavioral therapy for insomnia (CBT-i) is proven to effectively improve sleep [34] and may consequently also improve depression [35].

As mentioned before, a depression is a fall risk increasing condition. Hence, in addition to (non) pharmacological treatment of the depression, we recommend to perform a fall risk stratification followed by a multifactorial fall risk assessment in those at high risk of falling. In accordance with the current guidelines, this encompasses the development of an individualized multidomain intervention to minimize fall risk in these patients [36]. A part of this assessment is performing a multidisciplinary medication review [37]. In a medication review a physicist and pharmacists enumerate a patient’s medications and analyze it, taking into account (among others) effectiveness and adverse effects of the medications. If any FRIDs are identified which are suitable for reduction, substitution or cessation, a deprescribing plan can be made together with the patient and caregivers, taking into account their goals and expectations. Subsequently the deprescribing process has to be frequently reviewed [38, 39]. Deprescribing of psychotropic medications has several specific aspects to take into consideration regarding indications and risks, such as relapse and withdrawal [40]. Despite this, psychotropic medications should be considered for deprescription the same way as somatic medications in order to lower anticholinergic burden [40]. Research has shown that after multidisciplinary medication review in older psychiatric patients, somatic medications are more often discontinued than psychiatric medications [41]. We therefore recommend psychiatrists to not hesitate to collaborate with pharmacists or somatic physicians in order to optimize pharmacotherapy in these vulnerable patients.

Our study has several strengths and limitations. A major strength of our study is that we used harmonized data of two well designed large population-based cohorts, which resulted in a large sample. Using multiple cohorts also makes the results more easily generalizable to other populations of older persons, because of the sociodemographicly and geographically more diverse characteristics of the cohorts, although all cohorts are situated in the same country. Another strength is that we calculated interaction on both the additive and multiplicative scale, using a 2x2 table of effect sizes (table 4) with one common reference category. This is the preferred method for quantifying interaction [26], and considered superior to performing a stratified linear regression analysis. The reason for this, is that the latter has no common reference category, making it difficult to compare the effect of ACB on fall risk in the two strata [42].

A limitation of our study is its cross-sectional design, therefore no definitive conclusions about causality can be drawn. Because of this design, we do not know for certain whether patients were already using the reported medications and were suffering from depressive symptoms at the time of the fall. But because medications with anticholinergic properties are often used chronically, and depression often persists for longer period of time, particularly in older persons [43], we assume it is plausible both were present at the time of the fall. Next, data on falling was retrospectively gathered based on self-report. It is known that self-reported fall incidents are being under-reported [44], especially in cognitively impaired patients, because in this population recall bias is stronger. Our study found a lower percentage of participants who reported falling in the past year than might be expected in this population [45]. This potential underreporting may have led to an underestimation of the effect. Another limitation is that we were unable to adjust our analyses for cognitive functioning as a possible source of confounding. Both falls and depression are related to cognitive functioning [21], and there is evidence suggesting ACB might also be related to impaired cognitive functioning [46]. The AD*F*ICE\_IT dataset had MMSE scores available, however in the sample used for the current analyses 70% were missing. We were therefore unable to impute this variable. To overcome this issue, we tested for confounding in the subpopulations of LASA. As cognitive functioning was not found to be a confounder in the association between ACB, clinical depression and falls in this subset, we think it is unlikely that excluding MMSE scores from our analyses affected our findings. Next, we had relatively high missing values on CES-D score, BMI and blood pressure. We tried to overcome this issue by using multiple imputation using the missing variables. Furthermore, we used the CES-D to assess the severity of depressive symptoms. Although this is a widely used and clinically validated instrument [20], it is not suitable to make a clinical diagnosis of depression. Compared to structured DSM interviews by a trained professional, the CES-D will give an overestimation on the number of patients with a putative, clinical depression [47]. This means that participants with a clinical depression as indicated by the CES-D score, may not be diagnosed as such by a clinician. Despite this, the CES-D gives a good estimation of the severity of depressive symptoms [20]. This means the effect of clinical depression on fall risk may have been stronger if it was diagnosed using a structured interview. Besides this, selection bias theoretically might have occurred because the participants with depression may have been less motivated to participate in the study, leading to underrepresentation of clinically depressed individuals in our sample. However our finding that 11% of the subjects had clinically significant depression corresponds to previous studies using self-report instruments [4, 20].

To conclude, our cross-sectional study showed a synergistic effect of the combination of ACB and depressive symptoms on fall risk. For those at high risk of falls, interventions aimed at reducing fall risk are warranted, including a medication review that addresses fall-risk increasing drugs. If clinical condition allows, and risk of relapse of depression is low, deprescribing of antidepressants should be considered. However, it is important to adequately treat depression, even with anticholinergic medication if necessary, because depression can have a major impact on quality of life and also affects fall risk. When treating an individual with depression, non-pharmacological options should also be considered. If pharmacological treatment is necessary anticholinergic burden should be taken into account, since this varies between antidepressants, even with equal effectiveness [3]. Fall risk can be lowered by deprescribing fall risk inducing drugs, including medicines with high(er) ACB. Studies with a longitudinal design are necessary to assess prospective fall risk caused by the interaction between anticholinergic medications and depression in older persons, to further improve pharmacological strategies for the treatment of depression in older persons.

**Acknowledgements**

The author declares that there are no acknowledgements to be made in this work.

**Conflict of interest statement**

The authors have no competing interests to declare that are relevant to the content of this article.

**Funding statement**

No funding was provided for this particular study. For the funding of the establishment of the LASA cohort, the Rotterdam study and the ADFICE\_IT harmonized dataset we refer to the corresponding literature [8-10].

**Data availability statement**

The data that support the findings of this study are not openly available due to reasons of sensitivity. They are located in controlled access data storage at the Amsterdam Public Health Research Institute. Data are, however, available from the authors upon reasonable request and with permission from the Amsterdam Public Health Research Institute.

**References**

1. Henstra, M.J., et al., *The association between apathy, decline in physical performance, and falls in older persons.* Aging Clin Exp Res, 2019. **31**(10): p. 1491-1499.

2. Darowski, A., S.A. Chambers, and D.J. Chambers, *Antidepressants and falls in the elderly.* Drugs Aging, 2009. **26**(5): p. 381-94.

3. van Poelgeest, E.P., et al., *Depression, antidepressants and fall risk: therapeutic dilemmas-a clinical review.* Eur Geriatr Med, 2021. **12**(3): p. 585-596.

4. Blazer, D.G., *Depression in Late Life: Review and Commentary.* The Journals of Gerontology: Series A, 2003. **58**(3): p. M249-M265.

5. Green, A.R., et al., *Drugs Contributing to Anticholinergic Burden and Risk of Fall or Fall-Related Injury among Older Adults with Mild Cognitive Impairment, Dementia and Multiple Chronic Conditions: A Retrospective Cohort Study.* Drugs Aging, 2019. **36**(3): p. 289-297.

6. Tan, M.P., et al., *Use of Medications with Anticholinergic Properties and the Long-Term Risk of Hospitalization for Falls and Fractures in the EPIC-Norfolk Longitudinal Cohort Study.* Drugs Aging, 2020. **37**(2): p. 105-114.

7. Zia, A., et al., *Anticholinergic burden is associated with recurrent and injurious falls in older individuals.* Maturitas, 2016. **84**: p. 32-7.

8. van de Loo, B., et al., *Development of the ADFICE\_IT Models for Predicting Falls and Recurrent Falls in Community-Dwelling Older Adults: Pooled Analyses of European Cohorts With Special Attention to Medication.* J Gerontol A Biol Sci Med Sci, 2022. **77**(7): p. 1446-1454.

9. Ikram, M.A., et al., *The Rotterdam Study: 2018 update on objectives, design and main results.* European Journal of Epidemiology, 2017. **32**(9): p. 807-850.

10. Huisman, M., et al., *Cohort Profile: The Longitudinal Aging Study Amsterdam.* International Journal of Epidemiology, 2011. **40**(4): p. 868-876.

11. Boustani, M., et al., *Impact of anticholinergics on the aging brain: a review and practical application.* 2008.

12. Lisibach, A., et al., *Quality of anticholinergic burden scales and their impact on clinical outcomes: a systematic review.* European Journal of Clinical Pharmacology, 2021. **77**(2): p. 147-162.

13. Salahudeen, M.S., S.B. Duffull, and P.S. Nishtala, *Anticholinergic burden quantified by anticholinergic risk scales and adverse outcomes in older people: a systematic review.* BMC Geriatr, 2015. **15**: p. 31.

14. Richardson, K., et al., *Use of Medications with Anticholinergic Activity and Self-Reported Injurious Falls in Older Community-Dwelling Adults.* J Am Geriatr Soc, 2015. **63**(8): p. 1561-9.

15. Akgün, Ö., et al., *Anticholinergic Drug Use on Admission and the Risk of In-Hospital Falls in Older Hospitalized Patients.* Clin Interv Aging, 2022. **17**: p. 277-285.

16. Squires, P., et al., *Impact of Anticholinergic Medication Burden on Mobility and Falls in the Lifestyle Interventions for Elders (LIFE) Study.* J Clin Med, 2020. **9**(9).

17. Neal, S.R., et al., *Anticholinergic burden in middle-aged women and recurrent falls in later life: findings from the Aberdeen prospective osteoporosis screening study (APOSS).* Ther Adv Drug Saf, 2020. **11**: p. 2042098620929852.

18. Stewart, C., et al., *Anticholinergic burden measures and older people's falls risk: a systematic prognostic review.* Ther Adv Drug Saf, 2021. **12**: p. 20420986211016645.

19. Aizenberg, D., et al., *Anticholinergic burden and the risk of falls among elderly psychiatric inpatients: a 4-year case-control study.* Int Psychogeriatr, 2002. **14**(3): p. 307-10.

20. Radloff, L.S., *The CES-D Scale:A Self-Report Depression Scale for Research in the General Population.* Applied Psychological Measurement, 1977. **1**(3): p. 385-401.

21. Deandrea, S., et al., *Risk factors for falls in community-dwelling older people: a systematic review and meta-analysis.* Epidemiology, 2010. **21**(5): p. 658-68.

22. Folstein, M.F., S.E. Folstein, and P.R. McHugh, *“Mini-mental state”: A practical method for grading the cognitive state of patients for the clinician.* Journal of Psychiatric Research, 1975. **12**(3): p. 189-198.

23. *ATC/DDD Index 2023*. [Web Page] 2023; Available from: <https://www.whocc.no/atc_ddd_index/>.

24. White, I.R., P. Royston, and A.M. Wood, *Multiple imputation using chained equations: Issues and guidance for practice.* Stat Med, 2011. **30**(4): p. 377-99.

25. Twisk, J.W.R., *Inleiding in de toegepaste biostatistiek*. 2014: reed business education.

26. Knol, M.J., et al., *When One Depends on the Other: Reporting of Interaction in Case-Control and Cohort Studies.* Epidemiology, 2009. **20**(2): p. 161-166.

27. Knol, M.J. and R.H. Groenwold, *[Effect modification and interaction].* Ned Tijdschr Geneeskd, 2015. **159**: p. A8499.

28. VanderWeele, T.J. and M.J. Knol, *A Tutorial on Interaction.* Epidemiologic Methods, 2014. **3**(1): p. 33-72.

29. Welsh, T.J., et al., *Anticholinergic Drug Burden Tools/Scales and Adverse Outcomes in Different Clinical Settings: A Systematic Review of Reviews.* Drugs & Aging, 2018. **35**(6): p. 523-538.

30. Rebecca King, S.R. *Anticholinergic Burden Calculator*. Available from: <http://www.acbcalc.com/>.

31. Cuijpers, P., et al., *Psychotherapy for Depression Across Different Age Groups: A Systematic Review and Meta-analysis.* JAMA Psychiatry, 2020. **77**(7): p. 694-702.

32. Wilson, K., P.G. Mottram, and C. Vassilas, *Psychotherapeutic treatments for older depressed people.* Cochrane Database of Systematic Reviews, 2008(1).

33. Cooney, G.M., et al., *Exercise for depression.* Cochrane Database Syst Rev, 2013. **2013**(9): p. Cd004366.

34. Trauer, J.M., et al., *Cognitive Behavioral Therapy for Chronic Insomnia: A Systematic Review and Meta-analysis.* Ann Intern Med, 2015. **163**(3): p. 191-204.

35. Asarnow, L.D. and R. Manber, *Cognitive Behavioral Therapy for Insomnia in Depression.* Sleep Medicine Clinics, 2019. **14**(2): p. 177-184.

36. Montero-Odasso, M., et al., *World guidelines for falls prevention and management for older adults: a global initiative.* Age and Ageing, 2022. **51**(9).

37. van der Velde, N., et al., *European position paper on polypharmacy and fall-risk-increasing drugs recommendations in the World Guidelines for Falls Prevention and Management: implications and implementation.* Eur Geriatr Med, 2023. **14**(4): p. 649-658.

38. Woodward, M.C., *Deprescribing: Achieving Better Health Outcomes for Older People through Reducing Medications.* Journal of Pharmacy Practice and Research, 2003. **33**(4): p. 323-328.

39. Verduijn, M., et al., *Multidisciplinaire richtlijn Polyfarmacie bij ouderen.* Huisarts en wetenschap, 2013. **56**(8): p. 414-419.

40. Gupta, S. and J.D. Cahill, *A Prescription for "Deprescribing" in Psychiatry.* Psychiatric services (Washington, D.C.), 2016. **67**(8): p. 904-907.

41. Graveland, P.E., et al., *[Medication review in the mental health care service: experiences on long-stay units].* Tijdschr Psychiatr, 2016. **58**(4): p. 262-71.

42. Knol, M.J., W.R. Pestman, and D.E. Grobbee, *The (mis)use of overlap of confidence intervals to assess effect modification.* Eur J Epidemiol, 2011. **26**(4): p. 253-4.

43. Schaakxs, R., et al., *Associations between age and the course of major depressive disorder: a 2-year longitudinal cohort study.* Lancet Psychiatry, 2018. **5**(7): p. 581-590.

44. Peel, N., *Validating recall of falls by older people.* Accid Anal Prev, 2000. **32**(3): p. 371-2.

45. *Letsellastmodel 2021* [*https://www.veiligheid.nl/kennisaanbod/cijferrapportage/kerncijfers-letsels-nederland*](https://www.veiligheid.nl/kennisaanbod/cijferrapportage/kerncijfers-letsels-nederland). 2021, Veiligheid NL: Amsterdam.

46. Ruxton, K., R.J. Woodman, and A.A. Mangoni, *Drugs with anticholinergic effects and cognitive impairment, falls and all-cause mortality in older adults: A systematic review and meta-analysis.* Br J Clin Pharmacol, 2015. **80**(2): p. 209-20.

47. Kagee, A., et al., *Predicting caseness of major depressive disorder using the Center for Epidemiological Studies Depression Scale (CESD-R) among patients receiving HIV care.* Gen Hosp Psychiatry, 2020. **67**: p. 70-76.